LONDON COUNTY COUNCIL

THE DOSAGE OF ANTITOXIN IN DIPHTHERIA

Report of Departmental Committee appointed by the County Medical Officer of Health and School Medical Officer

The County Hall,
London, S.E.1
November, 1936

PUBLISHED BY THE LONDON COUNTY COUNCIL,
and may be purchased, either directly or through any Bookseller, from
P. S. KING AND SON, LIMITED,
14, GREAT SMITH STREET, VICTORIA STREET, WESTMINSTER, S.W.1,
Agents for the sale of the Publications of the London County Council.
1936

No. 3225. Price 6d.

22500837146

LONDON COUNTY COUNCIL

THE DOSAGE OF ANTITOXIN IN DIPHTHERIA

Report of Departmental Committee appointed by the County Medical Officer of Health and School Medical Officer

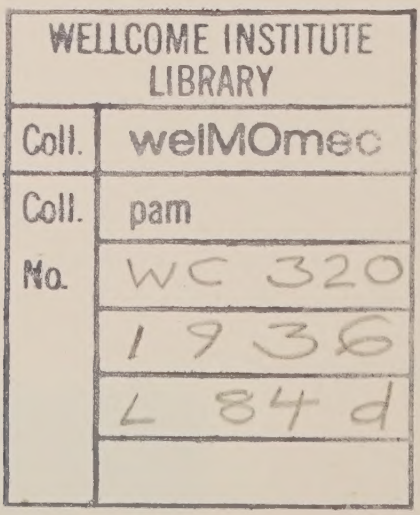
8000 (McC. 13706) 12.11.36

FOREWORD

While it is generally admitted that the marked reduction in the mortality and complication rates of diphtheria is due to the use of antitoxin, it is equally true that antitoxin is not always used in the manner and dosage calculated to give the best results. There is the widest diversity of opinion and practice, even in isolation hospitals. In many cases the importance of the time factor is not appreciated and injection is delayed; in others there is failure to assess properly the gravity of the disease and a sufficiently large initial dose is not given or is given by a route which does not promise the best results; in cases of a milder type a much larger dose than the condition necessitates is frequently given.

In an attempt to establish criteria for the guidance of the medical officers of the Council's hospitals a committee of acknowledged experts have prepared the following report which will, I hope, prove of value not only to their colleagues but to the medical profession in general.

FREDERICK MENZIES,
County Medical Officer of Health and School Medical Officer.



London County Council

PUBLIC HEALTH DEPARTMENT

REPORT OF THE DEPARTMENTAL COMMITTEE ON THE DOSAGE OF ANTITOXIN IN DIPHTHERIA

To Sir Frederick Menzies, K.B.E., M.D., Medical Officer of Health.

Constitution of the Committee.

The Committee was set up by you on 16th October, 1935, because of the lack of uniformity of practice in the Council's hospitals as regards dosage of diphtheria antitoxin, both for treatment and prophylaxis.

Members of the Committee.

You appointed the following to be members of the Committee :—

Dr. A. F. Cameron, Chief Medical Superintendent, Infectious Hospitals Service, Chairman ; Dr. J. S. Anderson, Medical Superintendent, Grove Hospital ; Dr. H. S. Banks, Medical Superintendent, Park Hospital ; Dr. E. H. R. Harries, Medical Superintendent, North-Eastern Hospital ; Dr. A. Joe, Medical Superintendent, North-Western Hospital ; and Dr. M. Mitman, Medical Superintendent, Eastern Hospital, Secretary.

The Committee's terms of reference were :—

Terms of reference.

To investigate the question of dosage of antitoxin in diphtheria and to recommend a schedule of doses for prophylaxis and for treatment of the various types of diphtheria.

In the letter of reference you stated :—

"While it is realised that no arbitrary standards can be laid down it is obvious that the experience of medical superintendents of fever hospitals should prove a very valuable guide."

Form of the report.

In the report the Committee have considered the factors which should influence the practitioner in his estimation of dosage and a schedule of doses has been recommended. In an appendix reference is made to certain points which occasionally demand consideration in the administration of serum but which do not strictly fall within the Committee's terms of reference.

Definition

Diphtheria is the reaction of the body to the presence of a virulent strain of corynebacterium diphtheriæ, of which the diagnostic criteria are the local formation of membrane and the development of local and systemic manifestations of toxæmia.*

Production of toxin in diphtheria.

The diffusible toxin of diphtheria is produced continuously at the site of the formation of membrane, and, passing into the blood stream, reaches the tissues of the body. The amount of toxin produced and absorbed varies with the site, extent and character of the local lesions. The avidity of toxin for living

* Definition of the Departmental Committee on "Nomenclature of Diphtheritic Infections." 1936 ; London County Council (P. S. King and Son, Ltd.).

cells is of a high order, and toxin is rapidly taken up from the circulation, so that the concentration in the blood stream is never very high.

Tissue-toxin combination.

The nature of the tissue-toxin combination is at present uncertain. A review of the available evidence suggests that in the highly susceptible, toxin becomes firmly fixed to the tissues within a few hours of its liberation. If this process is sufficiently intense, widespread or prolonged, it results in the death of the patient.

Aim of antitoxin treatment.

The effects of antitoxin are both direct and indirect. By neutralising toxin it reduces and, in favourable cases, abolishes toxæmia, and indirectly this action results in cessation of spread and early separation of membrane. The object in employing antitoxin is, therefore, to attack all existing toxin and any subsequently produced. The success in neutralising existing toxin depends upon the accessibility of that toxin to antitoxin. The capacity to deal with toxin subsequently produced depends upon the persistence of antitoxin in the blood.

Accessibility of toxin to antitoxin.

The existing toxin is distributed throughout the body, but is not uniformly accessible to antitoxin. There is, firstly, free circulating toxin, very small in amount, which is readily neutralised by antitoxin. Secondly, there is loosely bound toxin which has entered into the early stage of combination with the tissues ; the evidence suggests, but is not unequivocal, that this toxin can be influenced by antitoxin. Lastly, there is toxin in the final stage of firm combination with the tissues ; all the evidence points strongly to the view that toxin thus firmly united to living cells is entirely uninfluenced by antitoxin.

Time factor.

Since the last stage of the tissue-toxin combination is so firm as to be beyond the influence of antitoxin, it is of vital importance to bring antitoxin into action at the earliest possible moment in order to reduce the mortality and morbidity of the disease. It is possible to save the patient if a lethal dose of toxin has not yet entered into firm combination at the time antitoxin is administered. In any individual case it is impossible to make an accurate estimate of the amount of toxin which has been produced, absorbed and fixed ; but it is certain that in cases of severity the lethal dose is reached rapidly. The effectiveness of serum therapy, therefore, depends upon its earliest possible employment. The evidence is overwhelming that by far the most important single factor in the success of treatment with antitoxin is the time factor. " Every hour, every minute of delay—and this is not a figure of speech—is damaging. If the amount of toxin is near the lethal dose, life itself is at stake." (Schick.) In less severe cases the early administration of antitoxin reduces the incidence of complications and in so doing causes the disease to run a milder and shorter course.

Route of administration.

The object being to secure an effective concentration of antitoxin in the blood with the least possible delay, the route chosen for the administration is therefore of vital importance. At one end of

the scale of rapidity of action is the intravenous route, at the other the subcutaneous ; and in order between these two are the intraperitoneal and intramuscular routes. By the intravenous route antitoxin enters the circulation at once, the maximum concentration is immediately obtained and, for a given dose, is higher than the maximum reached by any other route. By all routes other than the intravenous, the time of maximum concentration in the blood and its level are determined by the rate of absorption from the site of injection. From a subcutaneous injection absorption is slow, the maximum concentration is relatively low and is not reached until 48 to 72 hours after administration. The rate of absorption from an intramuscular injection has been estimated to be 3 to 6 times as rapid as from a subcutaneous. Although the maximum attained is not much higher than from the subcutaneous, it is reached sooner, and therefore the concentration in the blood during the early hours after administration is much higher. Thus, as a rule, there is no justification for employing the subcutaneous route in any form of diphtheria, except in the special circumstances mentioned in the appendix. Although, on account of rapidity of action, the intravenous is the ideal route, not all cases of diphtheria necessitate its use. On the one hand, the mild character of the attack, and on the other the possibility of shock and the difficulty of administration to very young and restless children, especially those with collapsed veins, limit its application. Where rapid absorption of antitoxin is imperative, but the intravenous route is impracticable, a possible, but inferior, substitute is intraperitoneal administration. Where speedy absorption is less urgent, the route of choice is the intramuscular.

Single or divided doses.

The weight of evidence is definitely in favour of the view that a single dose is far more efficacious than the same amount in divided doses. With a single dose a higher and earlier concentration of antitoxin in the blood is attained. Further, if the severity of the case has been properly assessed and an adequate amount of antitoxin given by a suitable route, the quantity persisting in the blood after a single injection should be sufficient to continue beneficial effects until the active phase of the disease has passed. If, from the course of the disease, it is obvious that the first dose was insufficient, the case has not been properly assessed. It should be re-assessed and a further injection given. This may entail the administration of even larger amounts by a different route, although later doses, even of larger amounts, cannot wholly compensate for the deficiency of the first.

Assessment of severity.

The clinical manifestations of diphtheria fall into three classes :

(i) An initial local lesion associated with a varying degree of toxæmia, which, according to the severity of the case, may result in

(ii) signs of circulatory impairment ;

(iii) various paralyses.

A list of the possible manifestations and other factors from which the severity of a case is assessed is given below. Those which are most marked in the severe types of diphtheria are printed in capitals. It is of the utmost importance to emphasise that *one or more of the criteria of severity may be absent in a particular case, and that correct assessment is impossible unless due consideration is given to each and every one of the factors enumerated.*

(*a*) Local Signs.

(1) Membrane : Extent and Character.—In general, the more extensive the area covered by membrane, the more severe the case. Extensive membrane may, however, be present in the naso-pharynx and yet may not be detected on ordinary examination. Poorly-defined, glistening, semi-translucent membrane may be of more serious significance than the typical well-defined greyish-white membrane.

(2) Œdema.—Œdema of the fauces, uvula and pharynx is evidence of severity. It may be so marked as to obscure the view of tonsillar and pharyngeal membrane.

(3) Fœtor.—The typical fœtor of diphtheria is most obvious in the severe forms of the disease.

(4) Adenitis and periadenitis. — Whilst some degree of adenitis is common in diphtheria, the presence of periglandular swelling invariably means a severe attack. "Bull-neck" is the most extreme form of periadenitis.

(*b*) Systemic Manifestations of Toxæmia.

Although evidence can be obtained of the involvement of all tissues, consideration must be limited here to those clinical features which are capable of assessment. The most significant are :—

(1) *Muscular.*—Limpness, prostration.

(2) *Nervous.*—Lethargy, drowsiness, stupor, coma, restlessness, delirium.

(3) *Circulatory* (a) *Peripheral.*— pallor, varying from simple pallor to a waxy appearance with a cyanotic tinge. alterations in pulse : low tension ; rapid or slow ; irregular ; impalpable (very late). Coldness of extremities (very late). Hæmorrhages. (b) *Cardiac.*—In the first phase of diphtheria, cardiac signs are those common to any toxæmia. Characteristic signs occur later, but as the two phases often overlap, the signs are set out for completeness. It must be recognised that such signs are indicative of a severe attack and, by the time most of them appear, antitoxin therapy is of little avail. Nausea, vomiting. Alterations in the character of the heart sounds, such as softness, shortening and reduplication. Alterations in rate, such as tachycardia, bradycardia (late), gallop rhythm (very late). Irregularity

of the heart. Displacement of the apex downwards and outward, with increase of cardiac dullness. Enlargement of the liver. Precordial and abdominal pain (very late).

(4) *Urinary.*—Albuminuria, ANURIA.

In the assessment of severity, *pyrexia is not a sign upon which any reliance can be placed ;* indeed, the most toxic cases of diphtheria are frequently apyrexial.

(*c*) DURATION OF ILLNESS AND AGE OF PATIENT.

The *later* the case comes under treatment and the *younger* the patient, the more serious is the prognosis. Although, as a general rule, cases first seen after the third day should be regarded as late, the variable fatality of diphtheria must be remembered. In the mild types of the disease, several days may be available for successful antitoxin therapy ; in the severe types 24 hours may be the maximum.

(*d*) RESPONSE TO ANTITOXIN TREATMENT.

In a patient treated with an adequate amount of antitoxin by the appropriate route, a cessation in the advance of the disease should be apparent within 12 hours of intravenous administration, or 12 to 24 hours of intramuscular injection. Before these intervals have elapsed, an extension of the local and general signs is not necessarily evidence of failure of antitoxin therapy, but subsequent deterioration in the local or general condition must be regarded as evidence of inadequate or late treatment.

Classification.

In formulating a clinical classification of diphtheria, the Committee have adopted as a basis the anatomical classification set out in the Departmental Committee's Report on " Nomenclature of Diphtheritic Infections." What follows is based upon their report.

Diphtheria is typically a disease of the upper respiratory tract and is generally classified anatomically according to the site most obviously affected, *e.g.*, the fauces, the nose and the larynx. Since the membrane tends to spread, it is not unusual to find it involving more than one of these areas.

A classification based on purely anatomical considerations is defective as it does not necessarily give any indication of the degree of severity of the case. Since dosage is determined by severity, the aim should be, therefore, to formulate a classification based, not only on the site and extent of the membrane, but also on the evidence of local and systemic manifestations of toxæmia.

Cases of diphtheria may be divided into two main groups :—

(*a*) Respiratory diphtheria ;

(*b*) Non-respiratory diphtheria.

GROUP (*a*).—RESPIRATORY DIPHTHERIA.

(i) *Anterior nasal diphtheria.*—Commonly characterised by unilateral or bilateral nasal discharge, frequently blood-stained and often accompanied by excoriation of the surrounding skin.

In a proportion of cases membrane is visible in the anterior nares. Toxæmia is very rarely marked, the child as a rule being at most debilitated. Anterior nasal diphtheria responds readily to antitoxin treatment.

(ii) *Laryngeal diphtheria.*—This form may be primary, but is more often secondary to a faucial or naso-pharyngeal infection. It is characterised by symptoms of acute respiratory obstruction. Although the most striking immediate manifestations are due to the occlusion of the airway, the possibility of toxæmia must not be disregarded, even in the primary laryngeal form. Especially is this the case when the laryngeal involvement is secondary to a focus elsewhere. Antitoxin must be given promptly.

(iii) *Faucial (tonsillar) diphtheria.*—This term should be restricted to cases in which the membrane is confined to the tonsils, or tonsils and anterior pillars only. Once this area is passed by the membrane, the clinical severity approximates to that of the fourth class, *viz.*, naso-pharyngeal diphtheria. In tonsillar diphtheria the local evidence of toxæmia is usually slight, but subsequent systemic effects of toxæmia may ensue. In the absence of prompt treatment, the membrane is liable to spread rapidly and bring the case into class (iv).

When more than one of the anatomical areas classified above are involved, the severity of the case is correspondingly increased.

(iv) *Naso-pharyngeal diphtheria.*—This term was proposed by the Departmental Committee on " Nomenclature of Diphtheritic Infections " for cases in which the membrane extends beyond the tonsils and anterior pillars to either one or more of the following : palate, uvula, pharynx or post-nasal mucosa and its extensions. This Committee realise the difficulty in selecting a suitable name for this group, as the most *obvious* membrane may be palato-faucial, palato-pharyngeal or oro-pharyngeal. Nevertheless, this Committee agree that stress must be laid on the important fact that the primary focus may be post-nasal, especially in children under two years of age in whom primary tonsillar diphtheria is relatively uncommon. Owing to the difficulty of ascertaining by ordinary clinical examination the extent of the membrane in such cases, the true severity may not be appreciated, unless the possibility of the existence of this hidden naso-pharyngeal focus is realised. This Committee, therefore, accept the term naso-pharyngeal as the most suitable for this group.

Naso-pharyngeal diphtheria is frequently associated with a profuse, watery or sero-sanguineous discharge, which is sometimes described as a manifestation of toxæmia. It is more accurately considered as a sign of the extent of membrane in the nose. The surface area of the nasal mucosa is considerable, and a profuse discharge implies the involvement of an extensive area from which absorption of toxin can take place.

Naso-pharyngeal diphtheria is almost invariably accompanied by local and systemic manifestations of toxæmia ; in fact, the majority of the cases of severe toxic diphtheria fall within this group. All the important factors in the successful antitoxin therapy of the severer types of diphtheria—early administration of an adequate amount in a single dose by the intravenous route—apply with particular emphasis to the treatment of this type of case.

GROUP (*b*).—NON-RESPIRATORY DIPHTHERIA.

Non-respiratory diphtheria is characterised, as a rule, by chronic lesions, which, if untreated by diphtheria antitoxin, are apt to become progressive and intractable and to be followed by the clinical manifestations of toxæmia. Sores on the face, abraded surfaces, the genitals, the conjunctivæ, the lesions of chickenpox (as in some types of varicella gangrenosa), etc., may be the site of infection. In skin lesions which progress in spite of the most active local treatment, *e.g.*, some cases of paronychia, the possibility of diphtheria should be borne in mind, especially if the child has a nasal discharge or a sore nose.

These types are not often encountered and no definite rules can be laid down for antitoxin therapy, but if detected early a moderate dose is usually adequate. Owing to their rarity and their lack of characteristic features, they may escape early detection and, by the time the nature of the local lesion is determined, large doses may be necessary. The early recognition of diphtheria of the conjunctiva is particularly important because, if adequate treatment is delayed, rapid and complete destruction of the eye may result.

Dosage

General agreement has not yet been reached on the size of the therapeutic doses of antitoxin in the various types of diphtheria. The Committee are agreed that no rigid scale can be laid down. In drawing up the appended table, they have attempted to provide a sufficiently elastic range of dosage to permit of its acceptance by as large a body of authoritative opinion as possible.

In assessing a case of diphtheria in order to determine the amount of antitoxin necessary, the most satisfactory procedure is to adopt a simple classification of mild, moderate and severe. In the table the various anatomical types of diphtheria described under " classification " are first correlated with the degree of toxæmia with which they are commonly associated. The severity of the disease is then indicated. This permits a re-grouping into mild, moderate and severe diphtheria. To each of these is added a range of dosage and the route to be employed.

It is important that this table should be considered in conjunction with the notes appended, particularly those recommendations in the table to which asterisks have been added.

TABLE OF ASSESSMENT AND DOSAGES

Designation	*Site involved*	*Degree of toxæmia*	*Clinical severity*
Anterior nasal	Anterior nasal mucosa only	None Slight	Mild
Laryngeal	Larynx, with or without extension downwards to trachea and bronchi.	Slight Moderate	Mild Moderate Severe
Faucial	Tonsils and/or pillars	Slight Moderate	Mild Moderate
Naso-pharyngeal	Tonsils and pillars, with extension to one or more of the following: palate, uvula, pharynx, post-nasal mucosa and extensions.	Severe Very severe	Severe
Non-respiratory	Sores on the face, abraded surfaces, the genitals, the conjunctivæ, etc.	Very variable (see above)	Variable

Clinical severity	*Dosage of antitoxin*	*Route*
Mild	*2,000 to 10,000 units	Intramuscular
Moderate	15,000 to 30,000 units	*Intramuscular or intravenous
Severe	50,000 to *100,000 units	Intravenous

* For prophylaxis, 1,000–2,000 units intramuscularly. The duration of passive immunity varies in individuals, but for practical purposes may be considered to last for 21 days.

Although suggesting a minimum therapeutic dose of 2,000 units, the Committee consider that this amount is indicated only in those cases where, as in hospital, constant supervision is possible. Where such supervision is not possible, it would be well to follow the advice given in the memorandum of the Ministry of Health (1922) which is "it is seldom safe practice to rely on any dose which is less than 8,000 units, whatever the age of the patient." Similarly, although it is rarely necessary to exceed the upper limit of 100,000 units, cases occasionally occur in which experience suggests that it is expedient to do so.

The importance of the intravenous route has been repeatedly stressed in this report. If after assessment it is decided that more than 20,000 units are necessary, the Committee are of opinion that the intravenous route should be employed wherever possible.

The therapeutic advantages of the single dose have also been emphasised in this report and the amounts recommended in the table are intended to be given in this way. If it is considered

necessary to give an additional dose, the assumption is that the initial assessment was incorrect or that subsequent events have modified the original view taken of the case. In such circumstances the additional dose should be given by the intravenous route to compensate in part for the delay in giving an adequate amount of antitoxin by a single injection at the beginning of treatment.

A body of evidence is accumulating as to the use of the intraperitoneal route for the administration of antitoxin. The Committee are of opinion that experience is not yet sufficiently extensive to warrant the making of any recommendations, except to suggest that this route may be employed where the intravenous route, although indicated, is impracticable.

Concentrated serum.

The use of concentrated serum has diminished considerably the incidence and severity of serum reactions, and has facilitated the administration of large doses of antitoxin. The Committee are convinced that, in the present state of our knowledge, it should invariably be employed. The use of concentrated serum has, however, paved the way to the administration of excessive doses; and the Committee feel it necessary to emphasise that, whilst it is better to give too much rather than too little, every effort should be made to assess the optimum amount on the lines suggested in this report.

APPENDIX

DANGERS ASSOCIATED WITH SERUM ADMINISTRATION AND METHODS OF AVOIDING THEM

General remarks.

The administration of a foreign serum which in practice means horse serum, occasionally causes unpleasant reactions in hypersensitive individuals. The hypersensitive state may have been set up by a previous administration of serum, but reactions, occasionally severe, appear in individuals to whom serum is given for the first time. In every case in which the question of hypersensitiveness arises, the risk of a reaction must be weighed against the danger of omitting or postponing antitoxin therapy. Upon this judgment will depend the decision as to whether special preliminary precautions are necessary, or whether the therapeutic dose should be injected immediately. Owing, however, to the extreme rarity of alarming reactions, the Committee are of opinion that the possibility of their occurrence should not influence the practitioner in his decision to give adequate amounts of serum with the least possible delay by any route that clinical conditions indicate. Nevertheless, there are certain factors which tend to the production of such reactions against which precautions may be advisable.

It is recognised that two of the most important factors influencing the frequency and severity of serum reactions are the quantity of serum protein injected and the route by which it is

administered. In the highly sensitive, *e.g.*, the rare "horse-asthmatics," alarming symptoms may be produced by a dose as small as one minim. Although reactions may follow the introduction of serum by any route, they are more commonly associated with intravenous administration.

Serum reactions.

The unpleasant reactions which may follow serum administration are :—

(1) *Serum disease and anaphylaxis.*—(*a*) The common type of serum disease which occurs typically in persons who have received serum for the first time, is sometimes unpleasant but never fatal. It appears after a latent period of 7 to 21 days, most frequently in the second week. With concentrated sera reactions are rarely severe and usually consist of pyrexia and an itching urticarial rash. The severe reactions which were not uncommon with unconcentrated sera are now rarely seen.

(*b*) The unusual types of serum disease are most likely to occur in those who have been previously injected. Whilst the common type described above is not unusual after re-injection, the most frequent effect of such re-injection is to shorten the latent period and increase the intensity of the reaction. If the effects appear within the first week (commonly 2 to 4 days) the reaction is described as "accelerated"; if within an hour, as "immediate." Such immediate reactions are often associated with more severe constitutional symptoms such as vomiting, rigors and collapse. Sensitivity, however, does not ordinarily develop until about 10 days after the primary injection, so that repeated injections may be given within this period. Thereafter sensitivity may be established. The more recent the primary injection the more likely are serum reactions to take on an unusual form. Although it is true that previous administration of serum, including that in prophylactics, may sensitise a patient, in general it may be said that there is little to fear from giving a second injection to any person who has not suffered severely from the first.

(*c*) Anaphylaxis (or its human counterpart) is rare and is confined to markedly sensitised patients, such as "horse asthmatics," who have never been previously injected. A few deaths have been recorded. A history of asthma, therefore, demands caution in the administration of serum.

(2) *Rigors and collapse following intravenous injections.*—The relationship of this type of reaction to those previously mentioned is doubtful. Although in many respects it resembles the "immediate" reaction, it would appear to be distinct, because it occurs in those who have had no previous injections and may appear after the intravenous administration of non-protein substances. It may be followed after a latent period by the common serum disease. The occurrence of these reactions is lessened by the use of a serum warmed to the temperature of the body and injected slowly.

(3) *Toxic effect of preservatives.*—The Committee have considered the available evidence as to the effects of preservatives and conclude that the amounts present in therapeutic doses of concentrated serum cannot be regarded as toxic.

(4) *Other unusual reactions.*—Abscess formation at the site of injection of serum must, for all practical purposes, be regarded as due to sepsis of external origin. A rigid aseptic technique is essential for all injections of sera.

The Arthus phenomenon and polyneuritis or paralysis due to serum have been described. Their extreme rarity is endorsed by the fact that no case has come within the experience of any member of the Committee.

Procedure advised.

The following procedure should be adopted whenever serum is to be given :—

(i) Prior to the injection, an enquiry should always be made for a history of :—

(*a*) asthma or allied conditions in the patient or family ;

(*b*) previous administration of any type of serum ; the approximate date should be elicited.

(ii) As a routine, a fresh solution of adrenalin (1 in 1,000) should be at hand. At the first sign of a reaction, the administration of serum should be stopped and not less than 5 minims of adrenalin injected subcutaneously and repeated if necessary. The practitioner may prefer to administer the adrenalin just before the serum or concurrently, but the Committee cannot recommend intravenous administration of adrenalin except in emergencies. Other methods of combating shock should be available when intravenous serum is given.

(iii) Serum should be warmed to the body temperature and injected slowly. In suitable cases dilution of the serum with saline or glucose-saline may minimise reactions.

Tests of sensitivity.

If it is considered desirable to test for sensitivity, for example in cases of asthma, the intradermal method should be used. The Committee recommend 0·2c.c. of a 1 in 10 dilution as the quantity to be injected. It is preferable to use the therapeutic serum for the test, as the alternative—normal horse serum—may contain more proteins likely to produce reactions than the serum to be injected, thus raising unnecessary fears. Distinction should, however, be drawn between dermal and general (constitutional) hypersensitiveness. No exact parallelism exists between the two. In consequence, a patient with a positive skin test may not react to a subsequent therapeutic injection. On the other hand, severe reactions have been reported in people with a negative skin test.

Desensitisation.

A practical alternative to a test of sensitivity is to use a small dose of serum as the first desensitising dose and as an index of sensitivity. It should be emphasized, however, that methods of desensitisation, like tests of sensitivity, cannot be relied upon.

It may be necessary to vary the procedure advised below, according to circumstances :—

(i) *History of previous administration of serum.*—Inject 0·5 c.c. of the therapeutic serum subcutaneously :—

(*a*) If no reaction results, follow up with the full therapeutic dose by the appropriate route in not less than half an hour.

(*b*) If a reaction occurs, repeat the dose of 0·5 c.c. subcutaneously at intervals of not less than half an hour, until the reaction is minimal ; then inject the remainder intramuscularly.

(ii) *History of asthma or allied conditions, or of reaction to previous administration of serum.*—Inject 0·2 c.c. of a 1 in 10 dilution of the therapeutic serum subcutaneously :—

(*a*) If within half an hour no reaction results, give 0·5 c.c. of undiluted serum intramuscularly. If this produces no reaction, give the full dose intramuscularly in not less than half an hour. The Committee do not recommend the intravenous route in asthmatics.

(*b*) If a reaction occurs, fractionate the dose and administer the fractions subcutaneously at intervals of not less than half an hour. When the reaction becomes minimal, try a small fraction intramuscularly before administering the remainder by this route. In the highly sensitive, sera from animals other than the horse must be employed.

A. F. Cameron,
Chief Medical Superintendent, Infectious Hospitals Service. (Chairman.)

J. S. Anderson,
Medical Superintendent, Grove Hospital.

H. S. Banks,
Medical Superintendent, Park Hospital.

E. H. R. Harries,
Medical Superintendent, North-Eastern Hospital.

Alex Joe,
Medical Superintendent, North-Western Hospital.

M. Mitman,
Medical Superintendent, Eastern Hospital. (Secretary.)